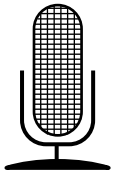

Darwinian medicine: Applications of evolutionary biology for veterinarians

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Abstract — Every medical phenomenon has both a mechanistic explanation and an evolutionary explanation. Veterinarians are accustomed to dealing with the mechanistic, the "what" or the "how", of various disease conditions, and applying treatment accordingly. Darwinian medicine is a field that addresses the evolutionary explanation, the "why" for various medical conditions. This review focuses on these Darwinian explanations and is divided into 4 main categories — host defenses, virulence, genetic conflict, and incomplete adaptation to a changing environment. Each of these areas is reviewed, with examples of evolutionary reasons for disease conditions. Consideration of adaptationist reasons for many of these disease phenomena should make veterinarians better clinicians, educators, and researchers.

Résumé — Médecine darwinienne : Application de la biologie évolutive à la médecine vétérinaire. Chaque phénomène médical procède de la mécanique et de l'évolution. Les vétérinaires ont l'habitude d'envisager les aspects mécaniques, c'est-à-dire le «quoi» et le «comment», de la maladie, et de choisir un traitement en conséquence. La médecine darwinienne s'attache aux aspects évolutifs de la maladie, au «pourquoi». Cet article porte sur les explications darwiniennes de la maladie, regroupées en quatre grandes catégories : les défenses de l'hôte, la virulence, le conflit génétique et l'adaptation incomplète à un environnement qui évolue. Chaque catégorie est examinée et accompagnée d'exemples d'explications darwiniennes de diverses maladies. Le fait d'envisager les explications darwiniennes de la maladie devrait faire des vétérinaires de meilleurs cliniciens, éducateurs et chercheurs.

(Traduit par M^me^ Suzanne Gasseau)

Can Vet J 2002;43:556–559

Darwinian medicine, a term coined in 1991 by Nesse and Williams (1,2), is the emerging field of study devoted to applying evolutionary biology principles to medicine. Whereas the traditional approach to medical problems is geared toward determining the proximate cause for disease, that is, the "what" and the "how," evolutionary or Darwinian medicine focuses on the ultimate or evolutionary reason for disease, that is, the "why." As professionals with the strongest training in comparative medicine and biology, veterinarians are well placed to consider aspects of evolutionary biology. As the great geneticist Dobzhansky stated over 50 years ago, "Nothing in biology makes sense except in the light of evolution" (3). Consideration of this adaptationist approach will make us more effective clinicians, educators, and researchers.

This paper introduces the concept of Darwinian medicine in a veterinary framework and provides food for thought for practitioners of veterinary medicine as to how this discipline is important in the basic understanding and control of various disorders. Examples in 4 main categories of evolutionary thinking — host defenses, virulence, genetic conflict, and incomplete adaptation to a changing environment are explored.

Host defenses and evolutionary medicine

One of the original tenets of evolutionary medicine, elucidated by Ewald in 1980 (4), was the importance of distinguishing which clinical signs are host defenses and which are pathogen offenses. Without understanding which clinical signs of disease are defenses, the clinician risks doing more harm than good. Many defenses are easily recognized as such, and practising veterinarians wrestle daily with the benefits versus the costs of interfering with an animal's defenses. Examples include the use of anti-inflammatory agents (especially

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There were no extra-institutional sources of funding involved with this work.

This paper was peer reviewed.

corticosteroids) in the face of possible infection; and cough suppressants, antiemetics, and antidiarrheals, each of which may suppress both the host defense in expelling harmful substances and the pathogen offenses in promoting their transmission.

Other defenses, such as the components of the acute phase response, are more subtle in how they function. The acute phase response is the set of metabolic, physiological, and behavioral changes brought on by severe infections and, to a lesser degree, by trauma and cancer. The more prominent components of the acute phase response include fever, sequestration of iron and zinc with increased serum copper, loss of appetite, catabolic alterations in metabolism, listlessness, and increased synthesis of acute phase proteins (C-reactive protein, ceruloplasmin, and fibrinogen). Noteworthy points from the viewpoint of evolutionary medicine are that the acute phase response is induced by the body's own cytokines, notably interleukin (IL)-1, tumor necrosis factor (TNF)-α, and IL-6, and that the acute phase response is present in all vertebrates. Components of it have been described in invertebrates (behavioral fever in crayfish and insects (5,6) and anorexia and malaise in insects (7)). Since one or more components of the acute phase response could easily have been selected out if they had proved to cause more net harm than benefit, the ubiquity of the acute phase response points to its apparently prominent role in host defense in a wide range of environmental conditions. The difficulty comes in determining exactly how each component of the acute phase response can be beneficial, especially since the harm is often easier to recognize.

There is strong evidence that fever is beneficial in control of infection, despite its metabolic costs and potential for self-harm (8). Sequestration of iron protects against bacterial and fungal infection (9), and the combination of fever and iron restriction has been shown to act synergistically in inhibiting bacterial infection (10). Local zinc sequestration by calprotectin from neutrophils has been shown to have antibacterial and antifungal activity (11,12). Hart (13,14), a veterinarian taking an adaptationist approach, noted that sickness behavior (listlessness with increased slow-wave sleep, inappetence, huddling, and decreased grooming) is clearly not due to pathogen-induced debilitation. Rather, sickness behavior is a programmed response and a significant component of the acute phase response. He elucidated a model suggesting how sickness behavior might have overall beneficial effects. Because an acute infection can be a life and death struggle for an animal, intense efforts should be made to devoting metabolic resources towards generating a fever, while at the same time ensuring that iron is sequestered from the bacteria or fungi. In this scenario, Hart argued that inappetence would both decrease ingestion of iron and, when coupled with listlessness, could reduce metabolically wasteful wandering activity and the convective heat loss associated with moving. Reduced activity might also reduce the likelihood of predation. Hart noted that while grooming activity is an important means of controlling ectoparasites, reduced grooming activity in illness might reduce energy use and, in mammals, evaporative water loss associated with licking.

While others have noted that anorexia might benefit in depriving extracellular pathogens of nutrients, such as iron and zinc (15), it has not been clear how nutrient deprivation could protect against intracellular infection without harming the host at least as much. However, noting that apoptosis (programmed cell death) can be an important host defense against intracellular infections, it has been hypothesized that the anorexia of infection can be beneficial against intracellular pathogens by depriving cells of nutrients, thereby making them more predisposed to apoptosis (16). Zinc restriction, in particular, is a proapoptotic stimulus (17). Cells already altered by being infected would be expected to preferentially undergo apoptosis, helping to control the infection. In this view, nutrient restriction could help inhibit both extracellular and intracellular pathogens (including viruses).

Ewald (18) has noted that much of the variability in effectiveness of generalized host defenses against specific pathogens may be a result of pathogen evolution. For instance, even the foremost experts on the adaptive value of fever in fighting infection note that the literature on the subject is mixed (8). Thus, even though in a "natural" setting fever may have a net protective effect (on a statistical basis), it would not be surprising to find specific pathogens that are not harmed by febrile temperatures or are even helped by such temperatures. Given the costs associated with fever (costs of generating it and of altered cell metabolism at a nonoptimal temperature), in patients infected with these pathogens, it would be beneficial to reduce the fever. Other specific pathogens may have evolved to avoid inducing fever, and patients infected with these pathogens might benefit from therapeutic fever induction. Similar principles apply with other defenses, all of which involve some costs to maintain or invoke. Any given defense may be vulnerable to a specific pathogen that avoids it or even uses it to its own advantage to the detriment of the host. Perhaps some day, medical knowledge will be such that host defenses can be therapeutically tailored to the specific pathogen, and certain defenses enhanced and others inhibited to optimize the host responses to the given pathogen.

Evolution and virulence

Evolutionary principles can be used effectively to analyze the evolution of virulence, particularly with regard to understanding the disease from the perspective of the pathogen. The familiar application of this principle is that pathogens evolve toward reduced virulence, since harming the host increases the likelihood of the pathogen becoming caught in a dying host before it (or rather its genes) can be transmitted to new hosts. However, Ewald (18) has used evolutionary thinking to show that this widely held principle is much too sweeping a generalization. One of the difficulties with the "evolution toward reduced virulence" principle is that pathogen populations acting benignly for their mutual benefit are susceptible to mutations for "cheating" (mutations that selfishly lead to faster pathogen replication). Factors complicating the genetic competition among pathogens in a host include strain genetic variability, mutation rate, and degree of vertical vs. horizontal transmission. Ewald has emphasized the strategic link between a

pathogen's transmissibility and its virulence. Where transmission is rapid, the pathogen need have little regard for the degree of its virulence; but where transmissibility is low, the pathogen benefits by maintaining the host's health, increasing the chance for transmission.

In some cases, the pathogen can increase its chances of transmission by altering the host's behavior. Rabies is a clear example of an infectious agent altering its host's behavior to enhance its transmission. An elegant example of pathogen-modified behavior involves the fluke *Dicrocoelium dendriticum,* which, by invading the subesophageal ganglion of its ant intermediate host, induces the ant to tightly clamp the top of grass stems. This facilitates the ant's being ingested by sheep or cattle, the fluke's definitive host (19). A more subtle example is the recently described finding that rats infected with *Toxoplasma* have altered behavior; specifically, they are less fearful of cats. Thus the pathogen increases its chances of delivery to the definitive host (20). However, simply the act of making the host sicker may facilitate disease transmission. The illness associated with malaria reduces the host's ability to fend off mosquitoes, thereby increasing the chance of transmission (21) — here, it is in the genetic interest of the *Plasmodium* sp. not to harm the mosquito vector. In modern clinical settings, cultural vectors, including methods of patient care, are a potential means by which a pathogen can induce its spread (22). In veterinary medicine, the result of making host animals sick is that either the animals are brought to a centralized hospital or a veterinarian visits the farm or facility. Either means of getting veterinary care has the potential of more readily promoting the spread of infectious agents.

Ewald (18) has noted that vector-borne diseases or diseases that induce actions that enhance their transmissibility tend not to have reduced virulence with time. Thus, behaviors that promote the spread of disease can allow enhanced virulence; conversely, behaviors that reduce transmissibility will lead to reduced virulence. Therefore, actively decreasing the disease transmissibility not only has its own benefits of preventing new infections and making the disease less prevalent, but gives the added benefit of reduced virulence (since there is increased selective pressure on the pathogen to reduce harm to the host until transmission can occur). This key insight has direct clinical relevance, since, as mentioned in the previous paragraph, veterinarians and their hospitals can play a major role in promoting or preventing pathogen transmissibility. Extending this principle of relating transmissibility with virulence, a recent mathematical model showed that vaccines that prevent infections can reduce both disease prevalence and virulence. On the other hand, vaccines that offer only antitoxin immunity are predicted to lead to increased disease prevalence and increased pathogen virulence, since the host is kept alive to propagate the pathogen and there is no selection against mutant pathogens having increased virulence (23).

Genetic conflict

A tenet of evolutionary biology is that the basic level of selection is the gene. However, selection typically occurs at the level of the individual carrying the gene. Genetic conflict can arise when the survival interests of interacting genes are not identical. Thus, even interactions between or within individual organisms that are primarily cooperative can have a degree of genetic conflict, which may have significant consequences.

Genetic conflict is particularly relevant to infectious diseases. The tremendously faster rate of evolution of pathogens compared with their hosts has led to the multiple levels of host defense and the incredible complexity of the immune system. Indeed, it has been proposed that a major benefit of sexual reproduction is to permit rapid genetic change as a means of helping to keep ahead of pathogens (24,25). Not only is there an evolutionary arms race between pathogens and hosts at the species level, but within an infected animal, there is evolution of the pathogen population and the host lymphocyte population (26). Genetic conflict can even occur within a single infected cell, as seen in the struggle between viral genes versus host genes for control of the cell's functional resources and machinery.

A form of genetic conflict with important implications occurs between parents and their offspring (27). The offspring shares only half of its genes with either parent or sibling. Therefore, the genes carried by this individual may benefit by extracting more resources than would be optimal for the parents to provide. This conflict is readily seen at weaning, where the weanling attempts to nurse for longer than the dam desires, thereby delaying her return to the reproductive cycle and lowering the probability of successfully raising more offspring. Haig (28,29) has extended the concept of parent-offspring genetic conflict to pregnancy and provided insights into the complexity of gestation not otherwise available. He has noted that much of the complex endocrinology associated with pregnancy can be understood in terms of the attempts by the fetus (especially the father's genes within the fetus) to extract more resources than the mother is prepared to give. For instance, in the fetus' effort to extract as many resources as possible from the dam, hormonal influences orchestrated by the fetus cause elevated blood pressure and glucose in the dam, which ensures that the fetus will receive more blood-borne nutrients. In humans, this conflict can be manifested as pregnancy hypertension and diabetes. Spontaneous abortions can be viewed as a form of maternal-fetal conflict. Early abortion of defective embryos or fetuses benefits the dam's overall reproductive success at the expense of the conceptus.

Genetic conflict between competing males is readily apparent in displays and aggression during the breeding season, as each male strives to be the inseminator. The conflict can also occur within the female reproductive tract as sperm competition. Rodents protect the probability of sperm success through formation of the copulatory plug, impairing subsequent insemination by another male. Not surprisingly, male rodents have developed methods of removing the copulatory plug of other males (30). Female choice is also a major factor in the genetic conflict involving breeding. The female's genes benefit by associating with the best male genes that are available. An enigma has been why so many sperm are required to fertilize an egg, given

that there has been more than ample time and selective pressure to have evolved a more efficient means of fertilization. Evolutionary biologists have argued that the complexity of the female reproductive tract and the requirement for huge numbers of sperm for fertilization are reflections of the genetic conflict involving passive female choice for high quality sperm (and hence offspring) (31). That is, just as female choice often demands costly courtship efforts of males, it also demands costly expenditures of nutrients in terms of sperm from males.

Incomplete adaptation to a changing environment

One of the main areas of inquiry in Darwinian medicine involves the concept that the human body is adapted to a Paleolithic environment but has not had time to adapt to modern lifestyles. Much has been made of human health problems concerning "non-natural" diet, reduced exercise, and modern postural problems with the notion that we have "Stone Age bodies" in a modern world (32,33). Examples of these problems can be seen in pets (overweight cats and dogs). But perhaps more relevant to veterinary medicine would be artificially driven evolution for economically useful physical traits that ultimately interfere with functioning under normal environmental conditions. Examples of conditions resulting from selecting for traits that push animals to the edge of physiologic capacity include metabolic diseases of dairy cows, musculoskeletal injuries of racehorses, dystocia problems in double-muscled cattle, and tendon disorders in domestic poultry. Many other veterinary problems arise from artificial selection for esthetically appealing traits that create medical conditions. These problems are readily recognized in various dog breeds: breathing and parturition difficulties in brachycephalic breeds, corneal irritation from excessive skin folds in certain breeds, and intervertebral disk disease in Dachshunds. The process of selective breeding can be seen as the struggle to fit naturally selected animals into a human-defined world.

Conclusion

In summary, evolutionary biology principles can enhance our understanding of numerous veterinary issues. Equally important, evolutionary biology provides a solid framework that greatly simplifies categorization of the vast amount of information we must cope with as veterinarians. In this brief introduction, we have cited a few examples with clinical relevance. Darwin (34) was prescient when he wrote at the conclusion of *The Origin of Species*, "In the future I see open fields for far more important researches." We see the application of evolutionary principles to veterinary medical thinking as one of those fields.

Acknowledgments

The authors acknowledge the helpful suggestions of the anonymous reviewers. CVJ

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